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NOVARTIS

Division of Dockets Management
Food & Drug Administration HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Docket 2007D-0396

Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation

December 20, 2007

Dear Sir, Madam:

Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG (NYSE: NVS), a world leader in pharmaceuticals and consumer health. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 98,000 associates and operate in over 140 countries around the world.

Novartis Pharmaceuticals Corporation researches, develops, manufacturers and markets leading innovative prescription drugs used to treat a number of diseases and conditions, in the oncology, central nervous system, organ transplant, cardiovascular respiratory and other therapeutic areas.

As one of the world's largest pharmaceutical manufacturers, Novartis has committed extensive resources to the handling of safety information for its investigational and marketed products. The proposed guidance has the potential to impact our pharmacovigilance operations and we appreciate the opportunity to offer comments.

General comments:

1. Novartis compliments the Agency for authoring a high-quality guidance on pre-marketing evaluation of the potential for drug-induced liver injury (DILI). The content is medically robust and meets the objective of helping the industry to identify hepatic safety signals in clinical development. It also provides more constructive detail and is more assertive in tone than earlier versions. We believe the guidance will serve to improve overall patient safety with new medicines and biological agents.

2. Please consider if this guidance might be an appropriate vehicle to also describe how investigational hepatotoxicity findings should be incorporated into the draft U.S.

prescribing information. More specific label instructions on when and how to monitor liver function in the post-approval setting might be of considerable use to clinicians.

3. The Agency may wish to consider and comment on the utility of existing toxicokinetic data and *in vitro* liver models (e.g. *ex vivo* isolated, perfused organs, cell culture) for predicting and assessing liver injury and also on how the results of these models may be used as guidance in monitoring clinical trials.

4. Please consider the value of adding recommendations on patient eligibility to the guidance. For example – hospitalization criteria and discontinuation rules for drugs that are known to be or are likely to be hepatotoxic.

5. In section 3 (Signals of DILI and Hy's Law) Novartis requests further clarification concerning the Agency's thoughts on monitoring and assessing studies for which many patients have LFT elevations with other risk factors for liver damage, and therefore do not meet component #3 of Hy's Law. In oncology studies, for example, it is common to enroll patients with advanced disease, including liver metastases, who have abnormal tests at baseline which could meet Hy's law but for whom treatment is essential.

6. Novartis recommends that the Agency comment on how to best analyze LFT data across all clinical trials conducted under an NDA or BLA. For example, is it preferable to use pooled or meta-analysis methodologies?

Specific comments:

1. (Page 5; Lines 202-220). The guidance on determining clinically significant elevations in ALT/AST are logical and medically sound. However, the ranges for ALT differ from the Common Toxicity Criteria grades 1-4. Novartis believes it is important to provide industry with standardized guidance on the use of this scale (or a similar one) for summarizing lab data in the NDA or BLA application.

2. (Page 6; Lines 249-263). The guidance should specify that acute viral co-infection (Hepatitis types A through E) must be ruled out in the evaluation of DILI. This evaluation should be done early based on the clinical picture. A suggestion is to add screening for hepatitis to the list of actions in section 4, page 8 of the guidance.

3. (Page 7; Line 272). Novartis recommends adding text after the sentence *"Pre-existing liver disease is not known to make patients more susceptible to severe DILI (Zimmerman, 1978, 1999).* Please consider adding: *"However, patients with compensated or decompensated cirrhosis may not be appropriate for testing except in situations where a drug is being evaluated for use in liver disease."*

4. (Page 12; Line 514-517). The guidance recommends that *"Any potential Hy's Law case should be handled as a serious, unexpected adverse event."* It is unclear what is meant by the word "potential". Novartis recommends deleting the word "potential", modifying the text to read: *"Any Hy's Law case should be handed as a serious, unexpected adverse event*

5. (Page 12; Lines 523-528). Novartis recommends that the Agency provide further guidance or recommendations on how to monitor and interpret early, transient changes in LFTs that do not meet Hy's Law criteria. Relevant examples from the Agency's experience would be valuable to the industry.

6. (Page 14; Lines 614-623). Novartis recommends modifying the last sentence in Section 3 to read: *"The contribution of sex, age, drug dose, or regimen and concomitant medications to the observed abnormalities should be explored."*

Thank you for providing us with the opportunity to comment on this guidance.

Sincerely,

Judith Sills,
Vice President & Global Head, Medical Safety Operations
Integrated Medical Safety